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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/349,489	12/02/1994	DAVID B. RING	0999.001	6479

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EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Office Action Summary	Application No.	Applicant(s)	
	08/349,489	RING, DAVID B.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,8 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In view of the appeal brief filed on Nov. 17, 2003, finality of the Office action mailed Dec. 18, 2002 has been withdrawn and PROSECUTION IS HEREBY REOPENED. New grounds of rejection are set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

5. The rejection of claims 1-3, 5, 8 under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration.

6. The rejection of claims 1-3, 8, and 15 under 35 U.S.C. 103(a) as being unpatentable over Hsieh-Ma et al. (Cancer Research, 1992), Weiner et al., (Cancer Research 1993), or Ring et al., (Breast Epithelial Antigens, 1991), in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al., (J. Exp. Med. 171:1957-1963, 1990) is withdrawn upon further consideration.

7. The rejection of claims 1-3, 8, and 15 under 35 U.S.C. 103(a) as being unpatentable over Hsieh-Ma et al. (Cancer Research, 1992), Weiner et al., (Cancer Research 1993), or Ring et al., (Breast Epithelial Antigens, 1991), in view of Fanger et al. (Critical Reviews in Immunology, 1992) or Snider et al., (J. Exp. Med. 171:1957-1963, 1990), and further in view of Ring, US Patent 6,054,561 is maintained.

New Grounds of Rejection:

8. Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Ring (U.S. Patent 5,959,084; issued Sep. 29, 1999; effective filing date Oct. 29, 1990).

Claims 1-3 and 8 are drawn to methods for inducing production of antibodies against a cancer antigen, comprising the step of administering a bispecific antibody to the patient in an amount sufficient to induce production of antibodies, wherein the bispecific antibody binds to a first antigen that is FcγRIII (CD16) and to a second antigen that is a caner antigen selected from the group consisting of c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein and an antigen recognized by a monoclonal antibody produced by hybridomas listed in claim 1. The claims

contain the recitation that the first or second binding sites are "derived" from various monoclonal antibodies. The second antigen may be present in the patient.

Claims 1 and 3 contain the recitation that the first binding site (claim 3) or second binding site (claim 1) is a "binding site derived from" monoclonal antibodies produced by various hybridomas. The recitation that the "binding site is derived from" a monoclonal antibody does not provide a structural limitation to the bispecific antibodies used in the claimed methods, because the phrase "derived from" is broadly interpreted to mean that the binding site may comprise as little as one amino acid in common with the binding site of the referenced monoclonal antibody.

Ring teaches bispecific antibodies that bind to FcγRIII and to p-glycoprotein and to methods of administering to patients (col. 24, line 63 – col. 25, line 24). Because the specification fails to teach that the amounts of bispecific antibodies that would be sufficient to produce antibodies in a patient are different from the amounts that would be sufficient to kill cancer cells when injected in a patient, it is assumed that because the steps of the method are the same (administration of a bispecific antibody), that the methods of Ring would inherently result in the production of antibodies. Thus, Ring teaches methods that are the same as that claimed.

9. Claims 1-3 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Weiner (Weiner, L.M. et al. Cancer Res. 53: 94-100, 1993, Jan. 1; previously cited).

Claim 8 is drawn to a method of claim 1, where the bispecific antibody is produced by hybridoma CRL 10197. The specification teaches that hybridoma CRL 10197 produces the 2B1 bispecific antibody (page 20, lines 17-22). Applicant has never stated on the record that the

hybridoma CRL 10197 was not publicly available prior to the filing date of the instant application. Furthermore, the parent antibodies, 520C9 and 3G8 appear to have been publicly available prior to the filing date of the instant application.

Weiner teaches a method of administering the 2B1 bispecific antibody (and how to make the 2B1 bispecific antibody (see reference 20)), to scid mice that have been injected with peripheral blood lymphocytes (PBL) (see page 97, 2nd col. – page 98, bridging paragraph). Thus, Weiner teaches the methods as claimed, because the Weiner's method step is the same as the method step of the claimed invention (administration of a bispecific antibody). Because the scid mice (which read on "patients") were also injected with PBL, the method of Weiner would inherently result in the production of antibodies. Thus, Weiner teaches the methods as claimed.

10. Claims 1-3, and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising the administration of bispecific antibodies comprising a first binding site that binds to FcγRIII and a second binding site that binds to the antigens c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein, does not reasonably provide enablement for methods comprising the administration of bispecific antibodies comprising a first binding site that binds to FcγRIII and a second binding site that binds to an antigen that is solely characterized as an antigen that binds to a monoclonal antibody produced by a hybridoma cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The claimed inventions are drawn to methods that comprise the administration of bispecific antibodies where one binding site of the bispecific antibody binds FcγRIII and the other binding site binds a cancer antigen. The cancer antigens are selected from the group consisting of c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein and antigens characterized as those recognized by monoclonal antibodies produced by the following hybridomas: ATCC Accession Nos HB 11830, HB 11769, HB 11768, HB 10798, HB 10802, HB 8490 HB 8485, HB 8691, HB 11052, HB 10812, HB 9496, HB 10789, HB 8488, HB 8662, HB 8697, HB 10785, HB 10796, HB 10793, HB 11752, HB 10795, HB 10801, HB 11751 and HB 10794. Additionally, the second binding site comprises a binding site that is "derived from" a monoclonal antibody produced by one of several hybridomas.

The full scope of the claims is not enabled by the specification because, in the case of the antigens characterized in terms of the binding ability of a monoclonal antibody, the specification fails to describe the antigen and to put into the hands of the skilled practitioner the antigen so that other antibodies may be made that could be used to make the second binding site of the bispecific antibodies. The recitation that the second binding site comprises a binding site derived from a monoclonal antibody does not remedy the deficiency of the specification because the

phrase "derived from" is open to interpretation. In the broadest interpretation, a binding site that is derived from the binding site of a designated monoclonal antibody may have as little as one amino acid in common. Because the antigens are not described by structure or a combination of physical and chemical properties, the specification does not enable one of skill in the art to use the antigen to make monoclonal antibodies. Therefore, one of skill in the art is not enabled to use any other monoclonal antibody, other than one of the monoclonal antibodies listed in claim 1, to make a bispecific antibody having a second binding site that binds to a cancer antigen that is not a known cancer antigen. Without the ability to make the bispecific antibodies as they are presently claimed, one of skill in the art cannot practice the claimed methods as they are presently claimed.

In view of the lack of description of the structural, physical or chemical description of the antigens that are bound by the monoclonal antibodies recited in claim 1, and in view of the broad phrasing of the structure of the binding site, one of skill in the art cannot practice the claimed inventions with regard to the uncharacterized antigens because one of skill in the art cannot make a second binding site that binds to the uncharacterized antigen. This is because the structure of the second binding site is not defined and because the structure of the antigen is not described. If one of skill in the art cannot make the claimed bispecific antibodies, one of skill in the art cannot practice the full scope of the claimed inventions.

Applicant may obviate this rejection by amending the claims to more specifically define the structure of the second binding site of the bispecific antibodies that are to be used in the claimed methods.

11. Claim 15 is further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Because claim 15 is directed to methods where the bispecific antibody is administered to a patient not expressing the antigen to which the second binding site binds, the method of claim 15 reads on a prophylactic methods of tumor vaccination, and would require administration of the bispecific antibody prior to the development of tumors.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The claimed methods are broadly drawn to methods of preventing cancer by administering a bispecific antibody prior to the development of tumors. The specification provides working examples for the treatment of tumors already present in a patient, where the bispecific antibody comprises a second binding site that binds to an antigen expressed by the tumor. However, the specification lacks any working examples to demonstrating the administration of a bispecific antibody to individuals not yet having cancer. Therefore, the specification contains no guidance for determining the appropriate time prior to the development of tumors to begin the therapy, or for identifying patients at risk for developing those tumors. In

view of the above, one of skill in the art would be forced into undue experimentation for the purpose of determining appropriate times, and for identifying patients at risk. Therefore, one of skill in the art would not have a reasonable expectation of success in the practice of the claimed invention.

12. Claims 1-3 and 15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is for purposes of the 'written description' inquiry, "*whatever is now claimed*" (see page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See Vas-Cath at page 1116). In the instant case, the claimed inventions are methods comprising the administration of bispecific antibodies that are defined in terms of the antigen to which each of the binding sites binds. One binding site binds to FcγRIII and the second binding site binds to a cancer antigen that may be either c-erbB-2, HMW mucin, HMW mucin II, p-glycoprotein and an antigen recognized by various monoclonal antibodies as recited in claim 1. Written description of a generic antibody is dependent on written description of the antigen to which the antibody binds. In the instant case, the cancer antigens of claim 1 that are only characterized by the

monoclonal antibody to which they bind. Such a characterization fails to define any structural, physical or chemical characteristics of an antigen. Therefore, applicant is not in possession of the antigen, and not in possession of the entire genus of antibodies that bind to that antigen. If applicant is not in possession of the broad class of antibodies to a particular antigen, applicant is not in possession of methods of using the broad class of antibodies to make a bispecific antibody for use in the claimed methods. The recitation in claim 1 that the second binding site of the bispecific antibodies is characterized as comprising a binding site "derived from" an antibody secreted by various deposited monoclonal antibodies fails to define the bispecific antibodies of the claimed methods because "derived from" is interpreted broadly to mean that the binding site may have as little as one amino acid in common with the referenced monoclonal antibody binding site.

If the skilled artisan cannot envision the detailed chemical structure of the encompassed antigens that are used to define the binding characteristics of the bispecific antibodies used in the method claims, then conception of the claimed invention is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of manufacturing or testing the claimed process. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for making or testing it. One cannot describe what one has not conceived. See Fides v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGFs were found unpatentable due to lack of written description for the broad class. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112, is severable from its enablement provision. (See page 1115).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D. can be reached at (571) 272-0871.

Anne L. Holleran
Patent Examiner
March 5, 2004

Gary L. Kunz

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